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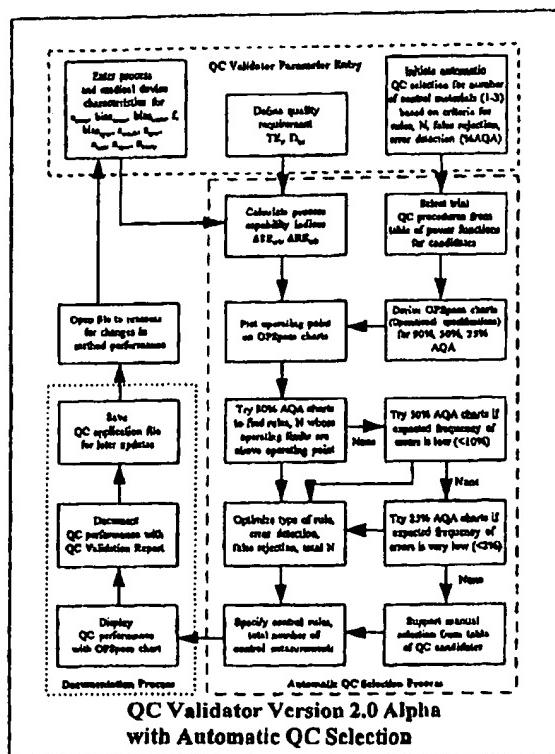
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(71) Applicant: WESTGARD QUALITY CORPORATION [US/US]; 112 Shore Road, Ogunquit, ME 03907 (US).	
(72) Inventors: WESTGARD, James, O.; 7614 Gray Fox Trail, Madison, WI 53717 (US). STEIN, Bernard; 112 Shore Road, Ogunquit, ME 03907 (US).	
(74) Agent: FARRELL, Kevin, M.; P.O. Box 999, York Harbor, ME 03911 (US).	

(54) Title: AUTOMATIC SELECTION OF STATISTICAL QUALITY CONTROL PROCEDURES

(57) Abstract

Disclosed is a computer implemented method for automating the selection of an analytical statistical quality control (QC) procedure. Inputs of a quality requirement and observed performance characteristics of a method of measurement are initially provided, together with a database of theoretical operating characteristics of statistical QC procedures. An appropriate quality-planning algorithm (either analytical or clinical) which relates the quality requirement, the observed performance characteristics of the method of measurement, and the theoretical operating characteristics of statistical QC procedures is also provided. Using predetermined QC selection criteria and selection logic, a computer is programmed to automatically select, based on the quality requirement, observed method performance, and operating characteristic of candidate QC procedures, a subset of control rules and numbers of control measurements which satisfy selection criteria and selection logic.



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AUTOMATIC SELECTION OF STATISTICAL
QUALITY CONTROL PROCEDURES

Background of the Invention

Health care providers in the United States have entered a new competitive era. Changes in government reimbursement policies have limited the amount of money that is paid for medical care. Payment of flat fees, based on Diagnostic Related Groups (DRGs), has effectively limited hospital and laboratory charges.

Support of Health Maintenance Organizations and similar prepaid medical plans has created new health-care organizations to compete with traditional providers. The new competitive marketplace puts pressure on a provider not only to reduce the costs of products and services but also, and at the same time, to improve their quality, to maintain or increase their share of the market. The effect on clinical laboratories is that performing more tests no longer guarantees more revenue or increased resources to support new tests and services. In addition, the quality of the laboratory's testing services that employ complex analytical processes, and their usefulness to the physician and patient must be at least maintained and, in many cases, improved.

In general, an analytical process includes a measurement procedure and a control procedure. The measurement procedure refers to the analytical method per se, i.e., the reagents, the instrument, and the step-by-step directions for producing an analytical result. The control procedure refers to that part of the process concerned with testing the validity of the analytical result to determine whether it is reliable and can be reported. The development and theoretical aspects of a control procedure are discussed, for example, by Westgard and Barry (Westgard, J.O. and Barry, P.L., *Cost-Effective Quality Control: Manage the quality and productivity of analytical processes*, AACC Press, Washington, DC (1986)).

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Improvements in an analytical process translate into reduced costs, higher productivity and improved quality of analysis for an implementing laboratory. In today's competitive environment, laboratories which focus on 5 improvements in such analytical processes are at a competitive advantage relative to those which do not.

Summary of the Invention

The subject invention relates to a computer implemented method for automating the selection of an 10 analytical statistical quality control (QC) procedure. Inputs of a quality requirement and observed performance characteristics of a method of measurement are initially provided, together with a database of theoretical operating characteristics of statistical QC procedures. 15 An appropriate quality-planning algorithm (either analytical or clinical) which relates the quality requirement, the observed performance characteristics of the method of measurement, and the theoretical operating characteristics of statistical QC procedures is also provided. Using predetermined QC selection criteria and 20 selection logic, a computer is programmed to automatically choosing, based on the quality requirement, observed method performance, and operating characteristic of candidate QC procedures, a subset of control rules and 25 numbers of control measurements which satisfy selection criteria and selection logic.

In another embodiment, the subject invention relates to a dynamic QC process for automatically changing the statistical QC procedure when there are changes in 30 performance of a method of measurement. In this embodiment, real-time statistical estimates of the performance characteristics of a method are provided through on-line sampling with an analytical instrument and this data is used to automatically select a QC 35 procedure.

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Brief Description of the Drawings

Figure 1 represents a logic diagram for automatic quality control procedure selection in both clinical and analytical formats.

5 Figure 2 represents a logic diagram for the dynamic, real-time application of automatic quality control procedure selection.

Figure 3 represents a quality control procedure selection criteria window.

10 Figure 4 represents a quality control procedure selection logic window.

Description of Preferred Embodiments

The present invention relates to a computer implemented method for automating the selection of a 15 statistical quality control procedure. The discussion which follows relates primarily to the application of the invention in the field of clinical diagnosis for human or animal healthcare. However, the invention has applications in other fields of use where comparatively 20 small numbers of controls plotted on a statistical control chart (e.g., the Levey-Jennings chart), are used to determine the acceptability of much larger numbers of samples tested by the same analytical method within the same time period.

25 The selection of a statistical quality control procedure is an essential element in the development of an analytical process. A statistical quality control procedure is necessary to alert an analyst when medically important errors occur. The control procedure should be 30 selected on the basis of the needed capabilities for error detection, as well as practical considerations related to its rate of false alarms, ease of use, training requirements, etc. The performance of the control procedure should be documented in quantitative 35 terms, so the chance of detecting the medically important errors is known.

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A direct way to check the quality of an analytical sample is by comparison to control samples having predetermined characteristics (e.g., concentration of an analyte) which behave similar to patient test samples.

5 Control sample, as used herein, refers to a control material or solution which can be purchased, or produced by dissolving appropriate concentrations of a solute in an appropriate solvent (typically buffered saline). Such materials are widely available as controls for clinical
10 chemistry analytes.

The analytical results obtained for control solutions (analyzed for purposes of quality control) are called control measurements or control observations. Such measurements are made using an analytical
15 instrument. In some control procedures, the individual results are plotted and interpreted directly. Many procedures, however, require calculations to be performed on the control measurements before the data can be used to test control status. These derived or calculated
20 values are called control statistics; for example, the mean of a group of six control measurements could be used as a control statistic.

Statistical techniques can be used to determine whether the control measurements are different from the
25 known values. Such procedures are known as statistical quality-control procedures, or simply, quality-control procedures. Control procedures are commonly implemented by plotting control measurements (or statistics calculated from those measurements) on control charts; a
30 control chart, therefore, is a statistical control model that provides a visual representation to aid interpretation. The American Society for Quality Control (ASQC) states that a control chart is "a graphical method for evaluating whether a process is, or is not, in a
35 'state of statistical control'".

By using control charts, analysts make decisions about the acceptability of the analytical results from individual analytical runs. Aliquots or samples from one

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or more stable control solutions are analyzed by the measurement procedure during each analytical run. The results are plotted on a control chart and compared with the control limits drawn on the chart; thus the analyst 5 determines whether an analytical run is in control or out-of-control and whether the results for the patients' samples in that run are to be reported.

According to the ASQC, control limits are the "limits on a control chart which are used as criteria for 10 signaling the need for action, or for judging whether a set of data does, or does not, indicate a 'state of control'". Control limits consist of upper and lower limits, which define a range of acceptable values. In general, an analytical run is judged to be in control 15 when the control measurements fall within the control limits, and out of control when the control limits are exceeded.

An analytical run can be defined as a period of time or series of measurements, within which the accuracy and 20 precision of the measuring system is expected to be stable; between analytical runs, events may occur causing the measurement process to be susceptible to variations which are important to detect (see also NCCLS Document C24-A, *Internal Quality Control Testing: Principles and 25 Definitions*, Vol 11 (No. 6), National Committee for Clinical Laboratory Standards, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898). The length of an analytical run must be defined appropriately for the specific analytical system and specific laboratory 30 application. The manufacturer should recommend run length for the analytical system and the user should define run length for the specific application. Thus, the length of an analytical run depends on the stability of the measurement procedure and its susceptibility to 35 errors.

However defined, an analytical run will include a certain number of patients' and control samples. An analytical run is that group of samples for which a

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decision is to be made concerning the validity of the measurements. The number of control measurements per run, N, is the actual number of control measurements available when judging the control status of the 5 measurement procedure. N is critical for determining the performance characteristics of a control procedure.

i. Analytical Quality Control

QC requirements can be defined in either clinical or analytical formats (or terms) and the methods and 10 compositions of the present invention relate to both categories. The logic for both the analytical and clinical embodiments are shown in Fig. 1. Referring first to the analytical embodiment, inputs of a quality requirement are essential. Analytical quality 15 requirements have been defined by the CLIA-88 proficiency testing (PT) criteria for acceptable performance (*Federal Register* 57(40): 7002 (February 28, 1992)). These criteria are presented in three different ways:

- as absolute concentration limits, e.g., target 20 value \pm 1mg/dL for calcium;
- as a percentage, e.g., target value \pm 10% for albumin, cholesterol, and total protein; and
- as the distribution of a survey group, e.g., target value \pm 3 standard deviations (SD) for 25 thyroid stimulating hormone.

In a few cases, two sets of limits are given, e.g., the glucose requirement is given as the target value \pm 6 mg/dL or \pm 10% (whichever is greater).

The CLIA PT criteria specify the total errors that 30 are allowable. The total error format is implicit because the CLIA-88 rules specify that only a single test is to be performed for each PT specimen. Under such conditions, the observed analytical error will be the total error due to both inaccuracy and imprecision. 35 Following is a list of the CLIA proficiency testing

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**criteria for the currently regulated analytes, based on
the February 28, 1992, Federal Register.**

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Routine Chemistry

	Test or Analyte	Acceptable Performance
	Alanine aminotransferase (ALT)	Target value \pm 20%
	Albumin	Target value \pm 10%
5	Alkaline phosphatase	Target value \pm 30%
	Amylase	Target value \pm 30%
	Aspartate aminotransferase (AST)	Target value \pm 20%
	Bilirubin, total	Target value \pm 0.4 mg/dL or \pm 20% (greater)
10	Blood gas pO ₂	Target value \pm 3 SD
	Blood gas pCO ₂	Target value \pm 5 mm Hg or \pm 8% (greater)
	Blood gas pH	Target value \pm 0.04
	Calcium, total	Target value \pm 1.0 mg/dL
	Chloride	Target value \pm 5%
15	Cholesterol, total	Target value \pm 10%
	Cholesterol (HDL)	Target value \pm 30%
	Creatine kinase	Target value \pm 30%
	Creatine kinase isoenzymes	MB elevated (present or absent) or Target value \pm 3 SD
	Creatinine	Target value \pm 0.3 mg/dL or \pm 15% (greater)
20	Glucose	Target value \pm 6 mg/dL or \pm 10% (greater)
	Iron, total	Target value \pm 20%
	Lactate dehydrogenase (LDH)	Target value \pm 20%
	LDH isoenzymes	LDH1/LDH2 (+ or -) or Target value \pm 30%
	Magnesium	Target value \pm 25%
25	Potassium	Target value \pm 0.5 mmol/L
	Sodium	Target value \pm 4 mmol/L
	Total protein	Target value \pm 10%
	Triglycerides	Target value \pm 25%
	Urea Nitrogen	Target value \pm 2 mg/dL or \pm 9% (greater)
30	Uric acid	Target value \pm 17%

Toxicology

	Test or Analyte	Acceptable Performance
	Alcohol, blood	Target value \pm 25%
	Blood lead	Target value \pm 10% or \pm 4 mcg/dL (greater)
35	Carbamazepine	Target value \pm 25%
	Digoxin	Target value \pm 20% or 0.2 ng/mL (greater)
	Ethosuximide	Target value \pm 20%
	Gentamicin	Target value \pm 25%
	Lithium	Target value \pm 0.3 mmol/L or \pm 20% (greater)
40	Phenobarbital	Target value \pm 20%
	Phenytoin	Target value \pm 25%
	Primidone	Target value \pm 25%
	Procainamide (and metabolite)	Target value \pm 25%
	Quinidine	Target value \pm 25%
45	Theophylline	Target value \pm 25%
	Tobramycin	Target value \pm 25%
	Valproic acid	Target value \pm 25%

Hematology

	Test or Analyte	White cell differentiation
50	Cell identification	Erythrocyte count

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	Hematocrit Hemoglobin Leukocyte count Platelet count 5 Fibrinogen Partial thromboplastin time Prothrombin time	Acceptable Performance 90% or greater consensus on identification Target \pm 3 SD based on percentage of different types of white cells Target \pm 6% Target \pm 6% Target \pm 7% Target \pm 15% Target \pm 25% Target \pm 20% Target \pm 15% Target \pm 15%
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Endocrinology

	Test or Analyte	Acceptable Performance
10	Cortisol	Target value \pm 25%
	Free thyroxine	Target value \pm 3 SD
	Human chorionic gonadotropin	Target value \pm 3 SD or (positive or negative)
15	T ₃ uptake	Target value \pm 3 SD by method
	Triiodothyronine	Target value \pm 3 SD
	Thyroid stimulating hormone	Target value \pm 3 SD
	Thyroxine	Target value \pm 20% or 1.0 mcg/dL (greater)

General Immunology

	Test or Analyte	Acceptable Performance
20	Alpha-1 antitrypsin	Target value \pm 3 SD
	Alpha-fetoprotein	Target value \pm 3 SD
	Antinuclear antibody	Target value \pm 2 dilution or (positive or negative)
	Antistreptolysin O	Target value \pm 2 dilution or (positive or negative)
25	Anti-Human Immunodeficiency virus	Reaction or nonreactive
	Complement C3	Target value \pm 3 SD
	Complement C4	Target value \pm 3 SD
	Hepatitis (HBsAg, anti-HBc, HBeAg)	Reactive (positive) or nonreactive (negative)
30	IgA	Target value \pm 3 SD
	IgE	Target value \pm 3 SD
	IgG	Target value \pm 25%
	IgM	Target value \pm 3 SD
	Infectious mononucleosis	Target value \pm 2 dilution or (positive or negative)
	Rheumatoid factor	Target value \pm 2 dilution or (positive or negative)
35	Rubella	Target value \pm 2 dilution or (positive or negative)

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In addition to the input of a quality requirement (as, for example, defined by the current CLIA standards), inputs of observed performance characteristics of a method of measurement are also provided in connection with the analytical embodiment of the present invention. In preferred embodiments, these observed performance characteristics include the following: stable imprecision observed (s_{meas}); stable inaccuracy ($bias_{meas}$); matrix inaccuracy ($bias_{matx}$); number of replicate samples (n_{samp}); z-value for maximum defect rate (z); and expected instability (frequency of errors, f). These terms are defined as follows:

- $bias_{meas}$ is the stable measurement inaccuracy;
- $bias_{matx}$ is the inaccuracy due to matrix effects;
- S_{meas} is the stable measurement imprecision;
- n_{samp} is the number of replicate samples analyzed and averaged to provide a single test result;
- z is the z value, usually set as 1.65 to specify that an analytical run will be rejected when the defect rate is a maximum of 5%; and
- f is the expected instability (or frequency of errors) which is used to indicate how often a given method has problems.

Using these input values, the computer is programmed to solve the analytical quality planning algorithm set forth below:

$$TE_{pt} = bias_{meas} + bias_{matx} + (\Delta SE_{cont} S_{meas}) / \sqrt{n_{samp}} + (zs_{meas} \Delta RE_{cont}) / \sqrt{n_{samp}}$$

where TE_{pt} is the analytical quality requirement referred to above in connection with the CLIA standards. The analytical quality requirement is in the form of an allowable total error, which is generally represented by the abbreviation TE_e . In the United States, this term can be replaced with TE_{pt} to represent the CLIA proficiency

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testing criteria for acceptable performance, which are analytical quality requirements of the total error form. Other terms in the analytical planning algorithm, not previously defined, include:

- 5 • ΔSE_{cont} is the change in systematic error (unstable
 inaccuracy) detectable by the QC procedure;
 and
 • ΔRE_{cont} is the change in random error (unstable
 imprecision) detectable by the QC
10 procedure.

In preferred embodiments of the present invention, default values and simplifying assumptions are established to facilitate application of the algorithm. For general application, particularly with automated or
15 mechanized analyzers, the quality planning algorithm may be simplified by combining the two bias terms to specify only a total bias, $Bias_{tot}$, and b) setting ΔRE_{cont} to 1.0 to optimize for systematic error rather than random error. The size of the systematic error that must be
20 detected to maintain quality within the specified requirement can be determined by solving for ΔSE_{cont} , then letting $\Delta SE_{cont} = \Delta SE_{crit}$ to denote this critically sized error.

RE optimization can be solved optionally. In the
25 preferred embodiment of the software, this requires activation through File and Preferences, ΔSE_{cont} is set to 0.0 to simplify the model and only the effect of unstable RE is considered.

Thus, the simplifications of the analytical quality
30 planning algorithm discussed above are used to calculate the critical sizes of systematic and random errors that need to be detected so the quality requirement will not be exceeded. Under these conditions, the term ΔSE_{crit} replaces ΔSE_{cont} and ΔRE_{crit} replaces ΔRE_{cont} .

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The critical systematic error, ΔSE_{crit} , is calculated as follows:

$$\Delta SE_{crit} = [TE_{pt} - | bias_{meas} + bias_{matx} |] (\sqrt{n_{samp}} / s_{meas})] - z$$

The critical random error, ΔRE_{crit} , is calculated as
5 follows:

$$\Delta RE_{crit} = TE_{pt} - | bias_{meas} + bias_{matx} | (\sqrt{n_{samp}} / z s_{meas})$$

Given an appropriate control rule, and the information calculated above from the analytical quality planning algorithm or algorithms derived from same, data
10 can be displayed graphically in a manner which facilitates optimization of a quality control procedure.

A control rule is a decision criterion for interpreting control data and making a judgment on control status (in control or out-of-control) (see e.g.,
15 Westgard et al., *Clin. Chem.* 23: 1857 (1977)). The theoretical operating characteristics of control rules and numbers of control measurements are described by power curves or probabilities for rejecting runs having different amounts of error present (see e.g., Westgard,
20 J.O., and Groth, T, *Clin. Chem.* 25: 394 (1979)). These power curves can be calculated based on probability theory or, alternatively, determined by computer simulation studies (see e.g., Westgard and Groth, *Clin. Chem.* 27: 1536 (1981)).

25 For example, the following control rules may be employed with individual-value charts where statistical control limits are drawn at certain multiples of the standard deviation(s) and measurements are plotted directly on the chart to assess control status:

- 30 • 1_{3s} indicates a run is rejected if 1 control value in the group of N control measurements exceeds control limits set as the mean + or - $3s$, where the mean and

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standard deviation are determined for the control material being tested.

- 2_{2s} indicates a run is rejected if 2 consecutive control values exceed the same control limit, which
5 is either the mean + 2s or the mean - 2s.
- R_{4s} is a range rule where a run is rejected if one control value exceeds the mean + 2s and another exceeds the mean - 2s.
- 4_{1s} indicates a run rejection if 4 consecutive control values exceed the mean + 1s or the mean - 1s.
10
- 10_x refers to a criterion where a run is rejected if 10 consecutive control values fall on one side of the mean.

15 Other control rules establish control limits having a specified probability for false rejection (P_{fr}). The actual control limits are determined by looking up factors in a table, then multiplying the standard deviation by those factors. Some examples are the
20 following:

- $l_{0.01}$ refers to a control chart where individual values in a group of N control measurements are plotted directly and compared to control limits set such that the probability for false rejection is
25 0.01, i.e., there is only a 1% chance that a good run will be falsely rejected.
- $X_{0.01}$ refers to a mean chart where the mean of a group of N control measurements is plotted and compared to control limits set such that the probability for
30 false rejection is 0.01.
- $R_{0.01}$ refers to a range chart where the difference between the high and low observations in a group of N control measurements is compared to a control limit set such that the probability for false
35 rejection is 0.01.

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Combinations of rules are indicated by individual rule abbreviations connected by a slash character, for example, $l_{3s}/2_{2s}$ indicates a multi-rule QC procedure that is made up of l_{3s} and 2_{2s} control rules, and $X_{0.01}/R_{0.01}$ indicates a QC procedure using both mean and range control charts.

For most control rules in common use in clinical laboratories, the control limits are set as the mean plus and minus constant multiples of the observed standard deviation, regardless of the number of control measurements being collected (N). However, for mean and range rules and single-value variable-limit rules, the control limits change as N changes. The actual control limits are calculated by multiplying the standard deviation by the factor given in the table below.

Factors for calculating control limits					
	Number of control measurements (N)				
Rule	2.24	2.39	2.50	2.64	2.74
$l_{0.05}$	2.81	2.93	3.01	3.13	3.21
$l_{0.01}$	3.27	3.36	3.44	3.52	3.59
$X_{0.05}$	1.39	1.13	0.98	0.80	0.60
$X_{0.01}$	1.82	1.49	1.29	1.05	0.91
$X_{0.002}$	2.19	1.78	1.54	1.26	1.09
$R_{0.05}$	2.77	3.31	3.63	4.03	4.29
$R_{0.01}$	3.64	3.63	4.40	4.76	4.99
$R_{0.002}$	4.37	4.80	5.05	5.37	5.58

In the computer-implemented method of the present invention, a database of operating characteristics is provided for a wide variety of control rules and classes of control rules, including single-rule fixed limit, single-rule variable limit, multirule, and mean and range. In addition, an editor function allows the user to incorporate the operating characteristics of additional control rules and numbers of control measurements by entry of the probabilities of rejection

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for specified increases in systematic (for ΔSE_{cont} values of 0.0, 0.5s, 1.0s, 1.5s, 2.0s, 3.0s, 4.0s; ΔRE_{cont} values of 1.0, 1.5, 2.0, 3.0, 4.0), as determined from probability theory or by computer simulation studies.

- 5 These operating characteristics may be represented graphically using a variety of visual tools which are known in the art. These visual tools include, for example, power function graphs, critical error charts and operating specification charts (referred to herein as
- 10 OPSpecs charts). Power function and critical error graphs plot the probability for rejection (P) on the y-axis and ΔSE (or ΔRE when optimizing for random error) on the x-axis. Critical error graphs display the size of the calculated medically important or critical systematic
- 15 or random errors on the power curves. OPSpecs charts plot allowable inaccuracy ($bias_{totl}$) on the y-axis and allowable imprecision (s_{meas}) on the x-axis. For a more detailed discussion of OPSpecs charts see, for example, Westgard, *Arch Pathol. Lab. Med.* 116: 765 (1992);
- 20 Westgard, *Clin. Chem.* 38: 1226 (1992); and Westgard, J.O., "Operating specifications for precision, accuracy, and quality control", *OPSpecs Manual — Expanded Edition*: Westgard Quality Control Corporation, Ogunquit ME, (1996).
- 25 Automatic QC (i.e., automatic control rule) selection is implemented on the basis of defined selection criteria and selection logic. In preferred embodiments, selection criteria employed to select candidate control rules from the database include 1) type
- 30 of control rule; 2) total number of control measurements per run; 3) probability of false rejections (also expressed in percent as a false rejection rate); and 4) probability of error detection (also expressed in percent as error detection rate, or as percent analytical quality
- 35 assurance (AQA)). Those skilled in the art are familiar with all of these parameters, and their significance with respect to control rule selection.

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In preferred embodiments, default settings are provided. These default settings are shown in the selection criteria window of Fig. 3. Users are, of course, free to change the default settings to define the types of control rules to be implemented (e.g., single rule fixed limits, single rule variable limits, multi-rule, mean/range rules), the total number of control measurements of interest (N's of 1, 2, 3, 4, 6 and/or 8), the maximum false rejection (10%, 5% or 1%), and the desired error detection rate (90%, 50%, 25%) (%AQA) for high, moderate and low instability. For example, with default settings, the program first attempts to select QC procedures having at least 90% error detection, regardless of the expected frequency of errors, but will select QC procedures having at least 50% error detection if an expected instability of less than 2% has been entered. By changing the default settings, a user can enable the program to select QC procedures having at least 25% error detection for an expected instability of less than 2%.

One of skill in the art will recognize that the options provided in the selection criteria window of Fig. 3 are somewhat arbitrary. For example, the desired error detection percentages, and minimum false rejection percentages provided could be percentages other than those provided.

Selection logic refers to the preferences, definable by the user, which determine the priority applied by the computer software in implementing the selection criteria discussed above. Default settings are again provided, as shown in Fig. 4. Users can modify default settings to define preference for low N vs. high N, single rule vs. multi-rule, and lower cost vs. higher error detection. For example, when 90% error detection can be achieved, default settings set preferences for the lowest N, single rule procedures which are the least expensive options. However, if 90% error detection can not be achieved, the default settings for 50% error detection provide

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preferences for the highest N multi-rule procedures having the highest error detection. As was stated in connection with selection criteria, the options provided in the selection logic window shown in Fig. 4 are merely examples. Those skilled in the art could design alternatives without the application of inventive skill.

Given required inputs for QC selection criteria and selection logic, the computer searches the control rule library for control rules and Ns satisfying selection criteria. The limits of allowable imprecision and inaccuracy for an OPSpecs chart are then derived for the candidate control rules and compared to the observed bias_{totl} and s_{meas} of the method (defined as the operating point). The 90% AQA charts are first checked to identify control rules and N whose operating limits are above the operating point. Each of these rules correspond to an appropriate QC procedure.

The computer is further programmed for control rule optimization. Control rule optimization means selecting:
20 1) an appropriate control rule from the database which has a high probability of detecting a systematic or random error in the patient samples results; 2) a low probability of false rejection (i.e., having to falsely retest the entire patient sample run due to a statistical
25 performance characteristic of the control rule); and 3) a minimum number of controls in the run of patient samples.

If none of the control rules provides a solution at 90% AQA, the computer is programmed to check 50% AQA charts. If control rule solutions are identified,
30 optimization is carried out as described above. If no solutions are identified at 50% AQA, 25% AQA charts are checked. If solutions are identified, control rule optimization is carried out. If no solutions are identified, the analyst is required to make a manual
35 selection.

When the computer completes optimization by the selection of a control rule and N, the analyst must review this selection and initiate documentation, or

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override this selection by making a manual selection of a different rule and N. This option for review and manual selection could be eliminated, but is considered desirable in order to maintain the professional interest 5 and responsibility of laboratory scientists. This selection completes the automatic QC selection process and provides the user with the information to prepare a control chart that can be used to plot control measurements from routine analytical runs. The control 10 rule selected dictates whether the patient sample measurements are judged to be in a state of control, or not.

Given the subject disclosure, it would be a matter of routine skill to select an appropriate computer system 15 and implement the claimed process on that computer system. This statement applies to all embodiments of the present invention, including the dynamic, real-time application discussed below.

ii. Clinical Quality Control

As stated previously, QC requirements can be defined 20 in either clinical or analytical formats. Having discussed the analytical format, the clinical format will now be addressed. The logic for the clinical embodiments of the subject computer-implemented methods (as well as 25 the analytical embodiments), are shown in Fig. 1. Clinical quality can be described as a medically important change in a test result that would affect the clinical interpretation of the test. The term decision interval (D_{Int}) is used to represent the size of the 30 change between two different test results that would cause different actions or outcomes in the medical application of the test result (Westgard et al., *Clin. Chem.* 37: 656 (1991)).

The clinical quality-planning model that is 35 incorporated in preferred embodiments of the present invention provides an approach which considers the potential variation of a test result due to biologic,

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pre-analytic, analytic, and quality control factors — all of which may contribute to the uncertainty of a single test result. The use of clinical quality requirements can be expected to be difficult because of the difficulty 5 in finding the necessary information for all the terms included in the model.

The most readily available recommendations are those provided by Skedzel et al. (*Am. J. Clin. Pathol.* 83: 200 (1985)). It is noted that information concerning 10 decision intervals is found in Table 1 of Skedzel et al., not in the table relating to medically allowable standard deviations, whose calculations do no not take into account the within-subject biological variation.

Quality planning algorithms describe the 15 mathematical relationship between the quality of a test result and the factors that can cause variation in that result. Some of the factors which must be considered are analytical. These include, for example, the imprecision and inaccuracy of the measurement procedure and the 20 sensitivity (or error detection capability) of the QC procedure. Others are pre-analytical, such as the within-subject biological variation that describes the changes in concentration due to normal biological variation. The clinical quality planning algorithm 25 employed in preferred embodiments of the present invention is shown below.

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$$D_{Int} = bias_{spec} + bias_{meas} + bias_{matx} + \Delta SE_{cont} s_{meas} / \sqrt{n_{samp}}$$

$$+ z \sqrt{\frac{s_{wsub}^2}{n_{test}} + \frac{s_{spec}^2}{n_{test} n_{spec}} + \frac{(\Delta RE_{cont} s_{meas})^2}{n_{test} n_{spec} n_{samp}}}$$

5 The clinical quality planning algorithm contains additional parameters, as compared with the analytical quality planning algorithm. Generally, these additional parameters relate to pre-analytical components of test variation. The clinical quality planning algorithm variables are defined as follows:

- 10 bias_{spec} represents sampling or specimen bias which allows for a pre-analytical component of systematic error which is entered as a percentage;
- 15 bias_{matx} is the inaccuracy due to matrix effects;
- 20 s_{wsub} represents the within-subject biological variation which is the standard deviation that represents the average biological variation of an individual subject which is entered as a percentage;
- 25 s_{spec} is the between specimen sampling variation which allows for the random variation between specimens, which is entered as a percentage;
- n_{test} is the number of tests drawn at separate times which are averaged to obtain a test result that will be interpreted;
- n_{spec} is the number of specimens which are drawn and averaged for each test;
- n_{samp} is the number of samples or replicates measured for each specimen (see page 8); and
- z-value defines the maximum defect rate that is allowed before the testing process is declared out-of-control (the default value is set at 1.65 which defines a maximum defect rate of 5%).

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Equations for the calculation of the critical systematic and random errors are derived in the same manner as was described for the analytical model. The equations will, of course, appear to be considerably more complex due to the inclusion of the additional terms defined above. Of the pre-analytical terms, it is most critical to account for within-subject biological variation (see e.g., Fraser, C.G., *Arch. Pathol. Lab. Med.*: 916 (1992)). Estimates of other terms may also be found in the literature (see e.g., Young, *Effects of Preanalytical Variables on Clinical Laboratory Tests*, AACC Press, Washington, DC (1993)).

Automatic QC selection in the clinical embodiment of the present invention is a process which is identical to that described above in connection with the analytical embodiment, but for the differences between the clinical and analytical algorithms.

iii. Dynamic, Real-Time Application of Automatic QC Selection

Automatic QC selection in the context of both analytical and clinical quality planning has been discussed above. Figure 2 shows the logic for a dynamic, real-time application of automatic QC selection which can be applied in either a clinical or analytical context. The initial steps in this application are identical to those discussed previously in sections i) and ii), above.

For example, with respect to an analytical application of the dynamic embodiment of the present invention, initial inputs of a quality requirement and observed performance characteristics of a method are provided. A quality control procedure (comprising a control rule and an N) is then selected automatically as previously described. As shown in Fig. 2, quality control data, generated by an analytical instrument, are transferred to a software program, either embedded within the medical device micro processor, or to a laboratory information system (LIS), or data management system

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- (DMS), or a stand alone PC program resident on a PC hard disk. The integration of these various components is a matter of routine skill. The control data is then converted to a control chart format in real time. The 5 control data is then analyzed on a continuing basis, and analytical statistical method of performance results are calculated. Numerical values for the method performance are input into a computer programmed to carry out the automatic QC procedure selection described above. In 10 this way, an appropriate QC procedure is automatically selected. The QC procedure which has been automatically selected is used to evaluate the control data for purposes of accepting or rejecting the patient samples in a run.
- 15 The introduction of a feedback loop for real time QC data enables an analytical measurement system, for example, to automatically select a higher N value, or a more sensitive control rule if method performance deteriorates. Alternatively, N would be automatically 20 decreased or a less sensitive control rule would be automatically selected if method performance were to improve.

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CLAIMS

1. A computer implemented method for automating the selection of an analytical statistical quality control (QC) procedure, the method comprising:
 - a) providing inputs of a quality requirement and observed performance characteristics of a method of measurement;
 - b) providing a database of theoretical operating characteristics of statistical QC procedures;
 - c) providing an analytical quality-planning algorithm which relates the quality requirement, the observed performance characteristics of the method of measurement, and the theoretical operating characteristics of statistical QC procedures;
 - d) providing QC selection criteria and selection logic;
 - e) automatically choosing, based on the quality requirement, observed method performance, and operating characteristic of candidate QC procedures, a subset of control rules and numbers of control measurements which satisfy selection criteria and selection logic.
2. The method of Claim 1 wherein the statistical QC procedure can be characterized by a control rule, control statistic, or control chart whose operating characteristics can be described in terms of probabilities of acceptance or rejection as a function of the size of systematic and random errors.
3. The method of Claim 2 wherein the control statistic represents the average of normal patient test results used to monitor errors or changes.

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4. The method of Claim 1 wherein the quality specification is an analytical quality requirement for the allowable total error, TEa.
5. The method of Claim 1 wherein the input parameters necessary for the analytical quality-planning algorithm are the stable imprecision observed (s_{meas}); stable inaccuracy ($\text{bias}_{\text{meas}}$); matrix inaccuracy ($\text{bias}_{\text{matx}}$); number of replicate samples (n_{samp}); and z-value for maximum defect rate (z).
6. The method of Claim 1 further comprising automatically selecting from among the subset of control rules in step e) the control rule which best satisfies the selection criteria and selection logic for type of control rule or control chart, total numbers of control measurements per analytical run, error detection rate, and false rejection rate.
7. The method of Claim 6 wherein the database of operating characteristics of statistical QC procedures comprises types of control rules and control charts selected from the group consisting of single-rule constant limits, single-rule variable limits, multi-rule with specified maximum number of runs, and mean/range rules.
8. The method of Claim 6 wherein the selection criteria and selection logic for the total number of control measurements per analytical run (N) includes 1, 2, 3, 4, 6, and 8 control measurements per run.
9. The method of Claim 6 wherein the selection criteria and selection logic for the rate of error detection are 90% or more, 50% or more, or 25% or more.

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10. The method of Claim 9 wherein the selection criteria and selection logic for error detection depend on the input for the observed instability of the measurement procedure.
11. The method of Claim 6 wherein the selection criteria and selection logic for the rate of false rejection are 10% or less, 5% or less, or 1% or less.
12. A computer implemented method for automating the selection of a clinical statistical quality control (QC) procedure, the method comprising:
 - a) providing inputs of a quality requirement and observed performance characteristics of a method of measurement;
 - b) providing a database of theoretical operating characteristics of statistical QC procedures;
 - c) providing a clinical quality-planning algorithm which relates the quality requirement, the observed performance characteristics of the method of measurement, and the theoretical operating characteristics of statistical QC procedures;
 - d) providing QC selection criteria and selection logic;
 - e) automatically choosing, based on the quality requirement, observed method performance, and operating characteristic of candidate QC procedures, a subset of control rules and numbers of control measurements which satisfy selection criteria and selection logic.
13. The method of Claim 12 wherein the statistical QC procedure can be characterized by a control rule, control statistic, or control chart whose operating characteristics can be described in terms of probabilities of acceptance or rejection as a

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function of the size of systematic and random errors.

14. The method of Claim 13 wherein the control statistic represents the average of normal patient test results used to monitor errors or changes.
15. The method of Claim 12 wherein the quality specification is a clinical quality requirement for a medically important change in the form of a decision interval, DInt.
16. The method of Claim 12 wherein the input parameters necessary for the clinical quality-planning algorithm are the stable imprecision observed (s_{meas}); stable inaccuracy ($bias_{meas}$); matrix inaccuracy ($bias_{matx}$); specimen bias ($bias_{spec}$); within-subject biological variation (s_{wsub}); sampling variation (s_{spec}); number of tests (n_{test}); number of specimens (n_{spec}); number of replicate samples (n_{samp}); and z-value for maximum defect rate (z).
17. The method of Claim 12 further comprising automatically selecting from among the subset of control rules in step e) the control rule which best satisfies the selection criteria and selection logic for type of control rule or control chart, total number of control measurements per analytical run, error detection rate, and false rejection rate.
18. The method of Claim 17 wherein the database of operating characteristics of statistical QC procedures comprises types of control rules and control charts selected from the group consisting of single-rule constant limits, single-rule variable limits, multi-rule with specified maximum number of runs, and mean/range rules.

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19. The method of Claim 17 wherein the selection criteria and selection logic for the total number of control measurements per analytical run (N) includes 1, 2, 3, 4, 6, and 8 control measurements per run.
20. The method of Claim 19 wherein the selection criteria and selection logic for the rate of error detection are 90% or more, 50% or more, or 25% or more.
21. The method of Claim 20 wherein the selection criteria and selection logic for error detection depends on the input for the observed instability of the measurement procedure.
22. The method of Claim 16 wherein the selection criteria for the rate of false rejection are 10% or less, 5% or less, or 1% or less.
23. A dynamic QC process for automatically changing the statistical QC procedure when there are changes in performance of the method of measurement, the method comprising:
 - a) providing inputs of a quality requirement and initial observed performance characteristics of a method of measurement;
 - b) providing a database of theoretical operating characteristics of statistical QC procedures;
 - c) providing quality-planning algorithms which relate the quality requirement, the observed performance characteristics of the method of measurement, and the theoretical operating characteristics of statistical QC procedures;
 - d) providing QC selection criteria and selection logic;
 - e) automatically choosing, based on the quality requirement, observed method performance, and operating characteristic of candidate QC

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procedures, a subset of control rules and numbers of control measurements which satisfy selection criteria and selection logic [for the desired rate of error detection and the desired rate of false rejection].

- f) providing real time statistical estimates of method performance characteristics through on-line sampling with an analytical instrument;
- g) repeating steps b)-f) above for a sequence of runs thereby automatically selecting a higher number of control measurements or more sensitive control rules when method performance deteriorates and decreasing the number of control measurements or changing to less sensitive control rules when method performance improves;
- h) implementing the selected statistical QC procedure through calculations and control charts;
- i) providing an assessment of the state of control and a decision about the acceptance or rejection of individual analytical runs based on the selected statistical QC procedure.

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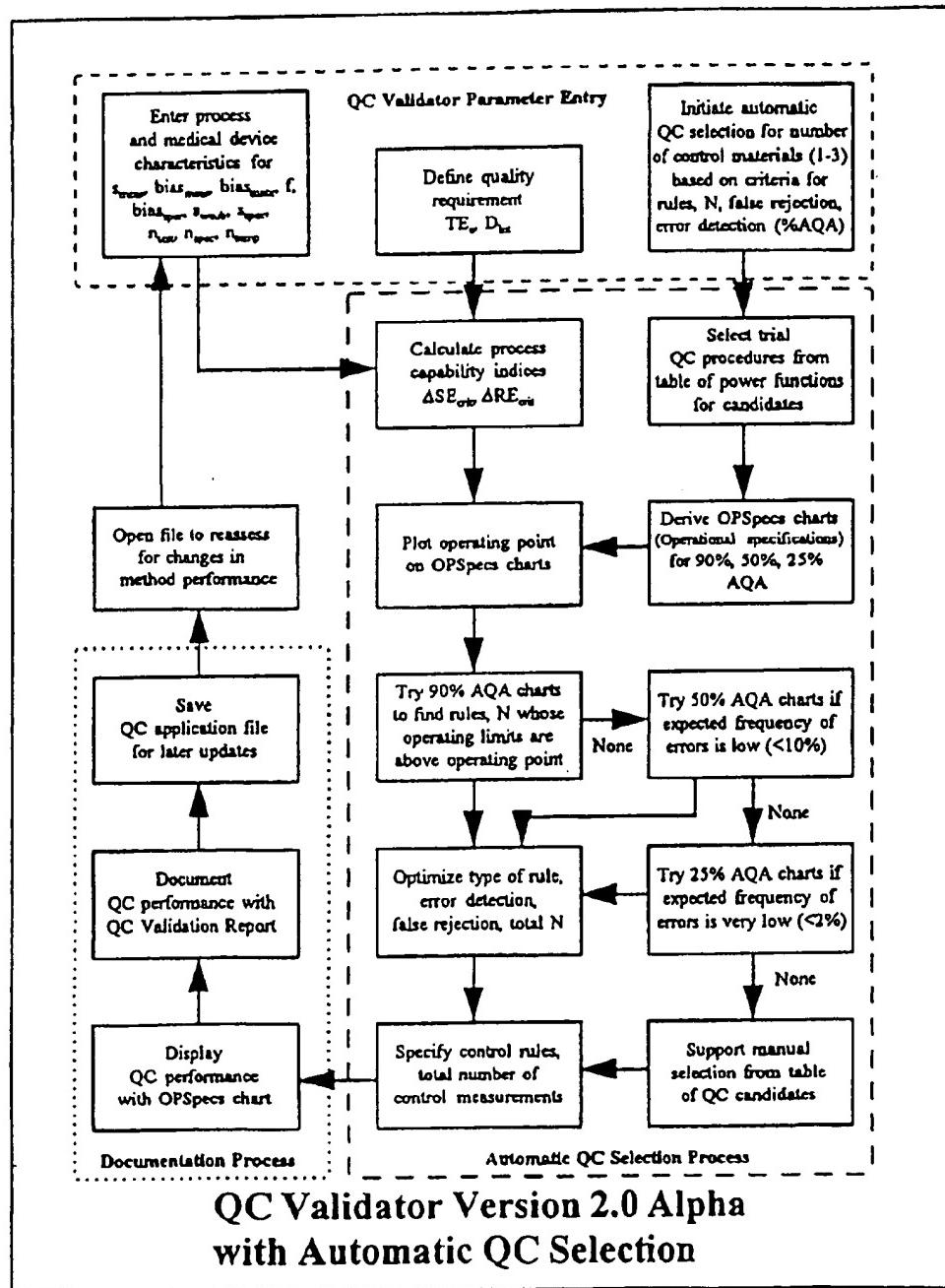


FIG. 1

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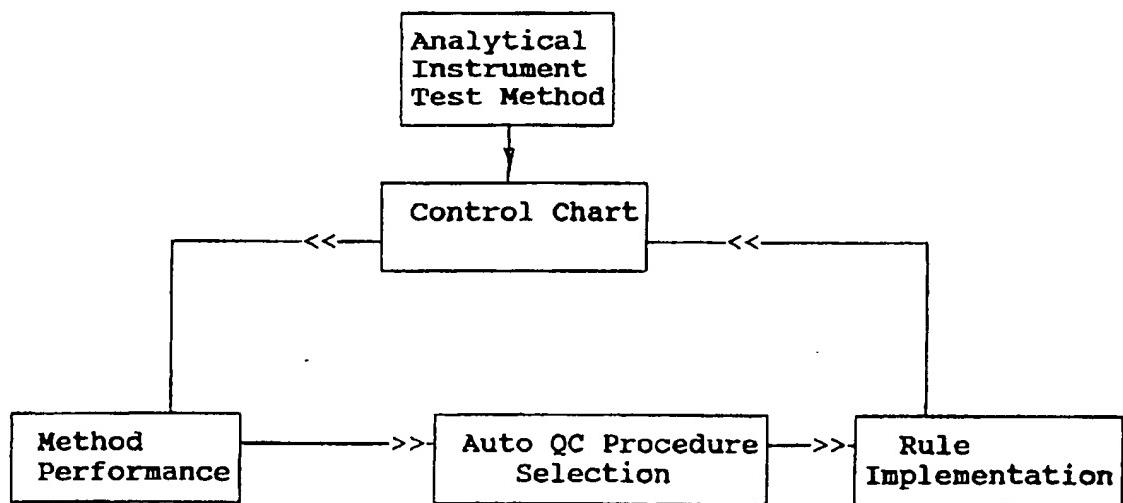


FIG. 2

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Automatic QC Selection Criteria

Control Rules

Single-rule fixed limit
 Single-rule variable limit
 Multirule - Max runs =

Total control measurements per run

N = 1 N = 4
 N = 2 N = 6
 N = 3 N = 8

False Rejection

1% or less
 5% or less
 10% or less

Error Detection (%QAQ)

90% preferred
 50% OK for low and moderate instability
 50% OK only for low instability
 25% OK only for low instability

FIG. 3

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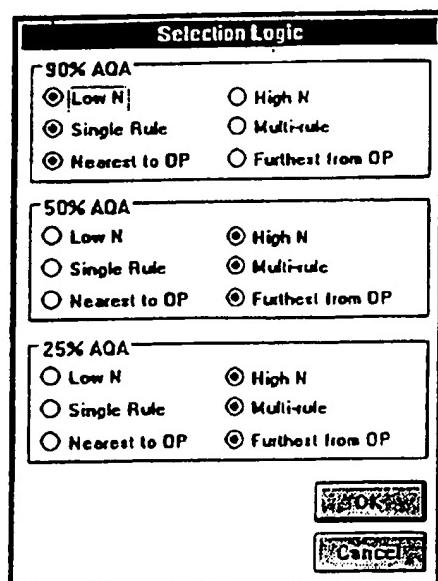


FIG. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/07517

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :G06F 17/60; G06G 7/52; G01N 31/00
US CL :395/207; 436/8

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 395/207; 436/8

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

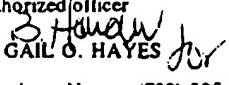
APS, DIALOG

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WESTGARD, J.O. et al.; Establishing and evaluating QC acceptability criteria; Medical Laboratory Observer, February 1994, v26, n2, page 1, lines 26-40; page 2, lines 12-41; page 3, lines 17-37; page 4, lines 15-46.	1-23.
Y	Abbott Datatrac Management System; Operations Manual; 1991; page i-vi, 1-1 through 1-6, 4-1 through 4-8, 4-49 through 4-54, 4-65 through 4-76, 6-1, 6-2, 6-41 through 6-50.	1-23
Y	Abbott DataTrac Management System, Interface/Troubleshooting Manual, 1991, pages i-vi, 2-1 through 2-10, 3-1 through 3-18.	23

Further documents are listed in the continuation of Box C. See patent family annex.

• Special categories of cited documents:		
'A'	document defining the general state of the art which is not considered to be part of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
'E'	earlier document published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
'L'	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
'O'	document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
'P'	document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search	Date of mailing of the international search report
20 JUNE 1997	09 JUL 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer  GAIL O. HAYES Jr.
Faxsimile No. (703) 305-3230	Telephone No. (703) 305-9711

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INTERNATIONAL SEARCH REPORTInternational application No.
PCT/US97/07517**C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	QC Validator Program Manual Version 1.1; WesTgard QC; 1993; pages 3-17 through 3-21, 4-1 through 4-6; 4-18 through 4-20; 4-23 through 4-26; 5-1 through 5-15.	1-23

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